REMARKS

1. Amendments to the Specification

The page number has been added to the top of the first page of the specification. No new matter is added.

2. Amendments to the Claims

Claim 27 has been amended. Support for the amendment is found in the specification at page 5, line 22.

Claim 30 has been amended to incorporate claim 31. Claim 31 has been cancelled. Support is found in the specification, page 5, lines 11-17.

Claim 32 has been amended for grammatical purposes.

Claims 33-35 have been amended. Support for the amendments is found in the specification at page 5, line 22.

Claims 36 has been amended. Support for the amendment is found in the specification at page 6, line 18.

No new matter has been added.

3. Claim Objections

The Examiner objects to claim 32 for reciting "by parenteral route" rather than "by a parenteral route." Applicants have amended the claim thereby obviating the objection. Applicants respectfully request that the objection be withdrawn.

4. Objections to the Specification

Applicants have amended the specification to add a page number on the first page as requested by the Examiner. Applicants request that the objection be withdrawn.

5. Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 30-36 as being indefinite. The Examiner states that the recitation of "comprising the sole step of administering either separately or simultaneously" because it is unclear how a sole step could permit separate administrations.

Applicants have amended the claim to recite "consisting of" and to omit the "sole step" language. Applicants submit that these amendments render the claim clear. Applicants request that the Examiner withdraw the rejection.

6. Rejections under 35 U.S.C. § 112, written description

The Examiner rejects claims 27-30 and 32-36 as failing to comply with the written description requirement. Applicants respectfully traverse.

The Examiner states that claims 27-29 recite an "association" of granulocyte colony stimulating factor (GCSF) and placental growth factor (PlGF). Applicants have amended claims 27-29 to replace "association" with "composition." Support for this amendment is found in the Specification at page 5, line 22 and in the claim 6 as originally filed. Applicants submit that one of skill in the art would have recognized that Applicants had possession of a "composition" at the time of filing. Applicants request that the rejection be withdrawn.

The Examiner states that the patient population in claims 30 and 32-36 is not supported by the specification as filed. Applicants have amended claim 30 to recite the patient population of claim 31, which the Examiner states is supported by the specification at page 5, lines 18-20. Applicants request that the rejection be withdrawn.

The Examiner states that the "intervals" in claim 36 is not supported by the specification. Applicants have amended claim 36 to recite "daily." Applicants submit that "daily" administration is supported in the specification page 6, line 18. Applicants accordingly request that the rejection be withdrawn.

7. Rejections under 35 U.S.C. § 103, obviousness

The Examiner rejects claims 27-32 and 34-36 as unpatentable over Robinson, Merck Manual, and Hattori. The Examiner also rejects claims 27-36 as unpatentable over Robinson, the Merck Manual, and Hattori, and further in view of Anderlini and Carmeliet. Applicants respectfully traverse.

Applicants submit that the combination of Robinson, the Merck Manual, and Hattori would not make the present invention obvious to one of skill in the art because one of skill would have no reasonable expectation that the combination of Robinson and Hattori would provide the increased mobilization of blood cells using the method or composition of the present invention. This is because Robinson specifically emphasizes that administration of recombinant GCSF has too much variability due to clearance issues and that the administration of Hattori, (i.e., the adenovirus expressing PlGF) is not predictive of the effects of the administration of PlGF protein directly.

Applicants submit that, based on Robinson, one of skill in the art would not have any expectation that administration of GCSF in combination with PlGF would be effective to increase mobilization of HSCs. Specifically, Robinson suggests that direct administration of recombinant GCSF protein "results in significant fluctuations in serum drug concentrations, as release from the injection site and clearance from the circulation occurs rapidly." (Robinson, page 537, col. 2, lines 22-27). Robinson also teaches that the goal is to achieve clinical efficacy with fewer injections. (Robinson, page 535, col. 1, lines 27-30). Thus, one of skill, reviewing Robinson, would not be inclined to use daily administration of recombinant GCSF protein as opposed to a treated protein, continuous infusion, or an adenovirus vector expressing GCSF (similar to that of Hattori).

Based on the teachings of Robinson, one of skill reviewing Hattori would also not be able to predict that recombinant PlGF protein would be effective to increase mobilization of HSCs. Instead, one of skill would either use one of the modifications to the protein or continuous infusion as described in Robinson, or the alternative presented in Hattori. Hattori discusses

administering an adenovirus vector which expresses PlGF. (Hattori, page 848, col. 2, lines 42-47).

However, the specification of the present application warns that administration with a recombinant adenoviral vector "presents several major differences from the direct injection of a purified factor, and might not be predictive of its effects when administered according to the modalities used in a clinical setting." (Specification, page 3, lines 23-26, emphasis added).

This hypothesis is borne out by qualitatively comparing the teachings in the specification against those in Hattori. Hattori discloses a 24-fold increase of CFU-Cs (progenitor cells capable of forming CFU colonies)(CF-GEMM, CFU-M, BFU-E) in BALB/c mice, three days after a single intravenous injection of Ad-PlGF, compared to the results obtained following administration of only one injection with Ad-null. (Hattori, Figure 4(c)).

In contrast, Example 2 of the present application teaches that mice which were injected intraperitoneally daily for **5 days** with recombinant mouse PlGF (rmPlGF) show almost the same almost the same total number of mobilized cells CFCs (CFU-GM, BFU-E, CFU-Mix) as the control mice. (Compare 8 ± 1 CFC/10^5 MNCs of the PlGF treated mice to 8 ± 1 CFC/10^5 MNCs of the control mice treated with PBS/MSA). Therefore, mice treated with PlGF alone were *not effective* to increase the total number of mobilized progenitor cells.

This is sharply contrasted by the results obtained using mice treated with recombinant PlGF protein and recombinant GCSF protein. Example 2 shows an approximate 1.5-fold increase of CFCs when small amounts of the two purified factors are administered as compared to administration of purified recombinant human GCSF (rhGCSF) alone. (Compare 115 CFC/10^5 MNCs in mice stimulated with both PlGF and GCSF to 76 CFC/10^5 MNCs of mice stimulated with GCSF alone).

Almost the same comparison can be made with the total white blood cells obtained following the administration of Ad-PlGF according to Hattori and the results obtained following

administration of the sole purified recombinant human PlGF (rhP1GF) according to the present invention. Applicants also point out that rhPlGF is decidedly more powerful than rmPlGF.

In fact according to Hattori the total WBCs in BALB/c mice treated 3 days after only one i.v. injection containing Ad-PIGF were about 2-fold higher than those treated with one i.v. injection, containing Ad-null (*see* Hattori, Figure 4a).

However, administration of rhPlGF alone is almost inactive to increase the total number of WBCs (2,296±1,235) in comparison to the basal value (2,165±929). But the same factor, when administered in amounts of 5pg/ml with rhGCSF, is able to increase the number of WBCs to 13,333 ± 2,023, namely about 7-fold the number of those treated with only rhG-CSF. (*See* Specification, Example 5).

The same comparison can be made for the other experiments reported in the specification wherein it results that PIGF alone is unable to increase the number of mobilized hematopoietic cells.

In view of the foregoing, a skilled person knowing the huge difference between an administration of an adenoviral vector expressing a protein and the administration of the purified protein, would not have found the present invention obvious.

The experimental data discussed above also represents the unexpected results achieved with the presently claimed invention.

The poor or almost zero effect of purified P1GF is also confirmed by Hattori, because the paper teaches the use of Ad-PIGF, rather than purified PIGF.

Therefore the skilled person would not have been able to predict from the disclosure of Hattori that purified PlGF had any activity or that the administration of the purified PIGF together with GCSF could result in a synergic activity. Applicants assert that such synergistic activity represents an unexpected result that is objective evidence of unobviousness of the present invention. Accordingly, Applicants request that the rejection be withdrawn.

With regard to references Anderlini and Carmeliet, the Examiner concedes that neither reference teaches the claimed composition or even purified PlGF and GCSF separately as it is used in the composition and method of the present invention. Accordingly, based on the arguments discussed above and the Examiner's own understanding of the additional references, one of skill in the art would not have found the present invention obvious. Thus, Applicants request that the Examiner withdraw the rejection.

Conclusion

In view of the above remarks, it is believed that claims are allowable.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell Reg. No. 36,623 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

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Respectfully submitted,

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Attachment: Substitute page 1 of the Specification